Patent
Serial No. 09/765,291
Attorney Docket No. 028723-243

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

JOE W. GRAY et al

Application No.: 09/765,291

Filed: January 22, 2001

For: CHROMOSOME-SPECIFIC STAINING TO DETECT GENETIC REARRANGEMENTS

Group Art Unit: 1655

Examiner: Marschal, A.

PRELIMINARY AMENDMENT

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination on the merits, please amend the above-cited application as follows:

IN THE CLAIMS

Please cancel Claims 1-126 without prejudice to or disclaimer of the subject matter contained therein.

Please add the following new claims:

–127. A composition comprising at least two probes, each labeled with a distinguishable label, for detecting a chromosomal aberration involving the BCR and ABL genes, said chromosomal aberration having an ABL gene side and a BCR gene side, wherein one of said probes hybridizes to the ABL gene side of said chromosomal aberration and the other of said probes hybridizes to the BCR gene side of said chromosomal aberration, wherein said probes hybridize to an aberrant chromosome wherein said probes are of sufficient length to be specifically detected in cytogenetic analysis.

128. A composition comprising at least two probes for detecting a chromosomal aberration, each probe labeled with a distinguishable label, wherein one of said probes hybridizes to a part of the ABL gene on one side of said chromosomal aberration and the other of said probes hybridizes to a part of the BCR gene on the other side of said chromosomal aberration, wherein said probes hybridize to an errant chromosome wherein said probes are of sufficient length to be specifically detected in cytogenetic analysis.

129. The composition of claim 128 wherein said probes hybridize within approximately 800 kb of each other in said aberrant chromosomes.

130. The composition of claim 127 wherein the labels comprise fluorescent labels.

131. The composition of claim 130 wherein the fluorescent labels are distinguishable under a microscope as different colors.

132. The composition of claim 127 wherein the probes hybridize with chromosomal DNA *in situ* in cells.

133. The composition of claim 132 wherein the cells comprise those in interphase of mitotic division.

134. The composition of claim 133 wherein the probes after hybridization are juxtaposed as doublets if a chromosomal aberration is present.

135. The composition of claim 127 wherein one of said probes hybridizes to at least a portion of the last exon of the ABL gene and the other of said probes hybridizes to at least a portion of exon I of the BCR gene.

136. The composition of claim 134 wherein the chromosomal aberration is further defined as comprising a translocation, said translocation formed by breakpoints which occur on the long arms of chromosomes 9 and 22.

137. The composition of claim 136 wherein the translocation breakpoints are further defined as occurring at the locations designated t(9;22)(q11;q34).

138. The composition of claim 137 wherein the translocation breakpoints are further defined to occur in the BCR and ABL genes respectively, and a fusion gene is formed by the translocation, and said fusion gene comprises portions of the BCR and ABL genes.

139. The composition of claim 132 wherein the cells comprise a sample of human tissue.

140. The composition of claim 139 wherein the human tissue sample comprises peripheral blood.

141. The composition of claim 139 wherein the human tissue sample comprises bone marrow.

142. The composition of claim 132 wherein the cells comprise a sample of cultured cells.

143. The composition of claim 127 wherein one of said probes hybridizes to the major breakpoint cluster region (M-bcr) of chromosome 22.

144. The composition of claim 127 wherein one of said probes hybridizes to the first exon of the BCR gene.

145. The composition of claim 127 wherein one of said probes hybridizes to at least a part of the last exon of the ABL gene.

146. The composition of claim 138 wherein the presence of said fusion gene is diagnostic or prognostic for acute lymphocytic leukemia (ALL).

147. The composition of claim 138 wherein the presence of said fusion gene is diagnostic or prognostic for chronic myelogenous leukemia (CML).

148. A kit for the detection of chromosomal aberrations, comprising a first and second nucleic acid probe, each labeled with a distinguishable label, said first probe specifically hybridizes to a part of the ABL gene on one side of said chromosomal aberration and said second probe specifically hybridizes to a part of the BCR gene on the other side of said chromsomal aberration, wherein said probes hybridize to an aberrant chromosome wherein said probes are of sufficient length to be specifically detected in cytogenetic analysis.

149. The composition of claim 127 wherein the aberrant chromosome is the Philadelphia chromosome.--

REMARKS

Entry of the foregoing, and early and favorable consideration of the subject application are respectfully requested.

By the present Amendment, Applicants have canceled Claims 1-126 in favor of newly added Claims 127-149. The new claims, which are substantially identical to the claims of U.S. Patent 6,025,126, recite compositions and kits for detecting a chromosomal aberration involving the BCR and ABL genes. These compositions and kits comprise at least two distinctly labeled probes, for detecting a chromosomal aberration involving the BCR and ABL genes, where the chromosomal aberration has an ABL gene side and a BCR gene side. One labeled probe in the composition or kit hybridizes to the ABL gene side of the chromosomal aberration, while a second, distinctly labeled probe, hybridizes to the BCR gene side of the chromosomal aberration. Such claims are at the very least entitled to an effective U.S. filing date of June 12, 1990, based on U.S. Application Serial No. 07/537,305.[1]

[1]The present application is a divisional of application Serial No. 08/487,974, filed June 7, 1995, which is a continuation of application Serial No. 08/342,028, filed November 16, 1994, which is a continuation of application Serial No. 08/181,367, filed January 14, 1994, which is a continuation of application Serial No. 08/054,353, filed April 28, 1993,which is a continuation of application Serial No. 07/537,305, filed June 12, 1990, which is a continuation-in-part of application Serial No.07/497,098, filed March 20, 1990, which is a continuation-in-part of application Serial No. 07/444,669, filed December 1, 1989, which is a continuation-in-part of application Serial No. 06,937, filed December 4, 1986; which is a continuation of application Serial No. 06/839,314, filed January 16, 1986.

Patent
Serial No. 09/765,291
Attorney Docket No. 028723-243

Exemplary written description support for Claims 127-149 in U.S. Application Serial No. 07/537,305 is set forth in Appendix A. This Preliminary Amendment is presented by Applicants in anticipation of filing a Request for Interference between the application identified in caption and U.S. Patent No. 6,025,126, in order to ensure compliance with 35 USC §135(b).

The Commissioner is hereby authorized to deduct any fees that are required by this paper to Deposit Account 02-4800.

Respectfully submitted,

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Dated: February 15, 2001

APPENDIX A

Exemplary support for new claims in 07/537,305, filed June 12, 1990.[2]

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
127. A composition comprising at least two probes, each labeled with a distinguishable label,	"In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of nucleic acid fragments, each fragment having a substantial fraction of its sequences substantially complementary to a portion of the nucleic acid for which specific staining is desired - the target nucleic acid, preferably the target chromosomal material. In general, the nucleic acid fragments are labeled by means as exemplified herein and indicated infra." p. 18, lines 14-20. "Section III *infra* describes methods of rendering the probe visible. Since multiple compatible methods of probe visualization are available, the binding patterns of different components of the probe can be distinguished – for example, by color. Thus, this invention is capable of producing any desired staining pattern on the chromosomes visualized with one or mor colors (a multi-color staining pattern) and/or other indicator methods." p. 36, lines 17-23.

[2]Applicants reserve the right to supplement this table as necessary or desirable.

Claims added by This Amendment	**Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]**
for detecting a chromosomal aberration involving the BCR and ABL genes, said chromosomal aberration having an ABL gene side and a BCR gene side, wherein one of said probes hybridizes to the ABL gene side of said chromosomal aberration and the other of said probes hybridizes to the BCR gene side of said chromosomal aberration,	"Specifically herein exemplified are chromosome specific reagents and methods to detect genetic rearrangements . . . that produce the BCR-ABL fusion which is diagnostic for chronic myelogenous leukemia (CML). Such chromosome specific reagents for the diagnosis of CML contain nucleic acid sequences which are substantially homologous to chromosomal sequences in the vicinity of the translocation breakpoint regions of chromosomal regions 9q34 and 22q11 associated with CML. Those reagents produce a staining pattern which is distinctively altered when the BCR-ABL fusion characteristic of CML occurs. Figure 11 graphically demonstrates a variety of staining patterns which, along with other potential staining patterns, are altered in the presence of a genetic rearrangement, such as, the BCR-ABL fusion." p 19, line 22 - p 20, line 8.
wherein said probes hybridize to an aberrant chromosome	"Such nucleic acid probes preferably comprise nucleic acid sequences that are substantially homologous to nucleic acid sequences in chromosomal regions that flank . . . breakpoints associated with genetic rearrangements." p. 19, lines 14-18

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
wherein said probes are of sufficient length to be specifically detected in cytogenetic analysis.	"The terms 'staining' or 'painting' are herein defined to mean hybridizing a probe of this invention to a genome or segment thereof, such that the probe reliably binds to the targeted chromosomal material therein and the bound probe is capable of being visualized." p 36, lines 9-12

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
128. A composition comprising at least two probes for detecting a chromosomal aberration, each probe labeled with a distinguishable label, .	"In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of nucleic acid fragments, each fragment having a substantial fraction of its sequences substantially complementary to a portion of the nucleic acid for which specific staining is desired - the target nucleic acid, preferably the target chromosomal material. In general, the nucleic acid fragments are labeled by means as exemplified herein and indicated infra." p. 18, lines 14-20. "Section III *infra* describes methods of rendering the probe visible. Since multiple compatible methods of probe visualization are available, the binding patterns of different components of the probe can be distinguished – for example, by color. Thus, this invention is capable of producing any desired staining pattern on the chromosomes visualized with one or more colors (a multi-color staining pattern) and/or other indicator methods." p. 36, lines 17-23.

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
wherein one of said probes hybridizes to a part of the ABL gene on one side of said chromosomal aberration and the other of said probes hybridizes to a part of the BCR gene on the other side of said chromosomal aberration,	"Specifically herein exemplified are chromosome specific reagents and methods to detect genetic rearrangements . . . that produce the BCR-ABL fusion which is diagnostic for chronic myelogenous leukemia (CML). Such chromosome specific reagents for the diagnosis of CML contain nucleic acid sequences which are substantially homologous to chromosomal sequences in the vicinity of the translocation breakpoint regions of chromosomal regions 9q34 and 22q11 associated with CML. Those reagents produce a staining pattern which is distinctively altered when the BCR-ABL fusion characteristic of CML occurs. Figure 11 graphically demonstrates a variety of staining patterns which, along with other potential staining patterns, are altered in the presence of a genetic rearrangement, such as, the BCR-ABL fusion." p 19, line 22 - p 20, line 8.
wherein said probes hybridize to an aberrant chromosome	"Such nucleic acid probes preferably comprise nucleic acid sequences that are substantially homologous to nucleic acid sequences in chromosomal regions that flank . . . breakpoints associated with genetic rearrangements." p. 19, lines 14-18
wherein said probes are of sufficient length to be specifically detected in cytogenetic analysis	"The terms 'staining' or 'painting' are herein defined to mean hybridizing a probe of this invention to a genome or segment thereof, such that the probe reliably binds to the targeted chromosomal material therein and the bound probe is capable of being visualized." p 36, lines 9-12

Claims added by This Amendment	**Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]**
129. The composition of claim 128 wherein said probes hybridize within approximately 800 kb of each other in said aberrant chromosomes.	"The genetic rearrangement of CML brings the DNA sequences homologous to the probes together on an abnormal chromosome, usually the Ph[1], and together in the interphase nucleus, as illustrated in Figure 8. The genome distance between the probe binding sites in the fusion gene varies among CML cases, ranging from 25 to 225 kb." p. 119, lines 20-24.
130. The composition of claim 127 wherein the labels comprise fluorescent labels.	"In the examples provided in Section VIII of this application, the probes are labeled such that a dual color fluorescence is produced in the staining pattern of said probes upon in situ hybridization." p 47, lines 16-19.
131. The composition of claim 130 wherein the fluorescent labels are distinguishable under a microscope as different colors.	"this invention is capable of producing any desired staining pattern on the chromosomes visualized with one or more colors (a multi-color staining pattern)" p. 36, lines 21-23.
132. The composition of claim 127 wherein the probes hybridize with chromosomal DNA *in situ* in cells.	"In the examples provided in Section VIII of this application, the probes are labeled such that dual color fluorescence is produced in the staining pattern of said probes upon in situ hybridization (fluorescent in situ hybridization (FISH)." p. 47, lines 16-19; *see also* Section IV, p. 74 ("In Situ Hybridization")
133. The composition of claim 132 wherein the cells comprise those in interphase of mitotic division.	"Preferably, the staining reagents of the invention are applied to interphase or metaphase chromosomal DNA by in situ hybridization." p. 23, lines 12-13

Claims added by This Amendment	**Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]**
134. The composition of claim 133 wherein the probes after hybridization are juxtaposed as doublets if a chromosomal aberration is present.	Figures 8 and 11c illustrate probes, after hybridization, juxtaposed as doublets when a chromosomal aberration is present. Figure 11 "section c) represents the use of a probe which binds to sequences which come together as a result of the rearrangement and allows for the detection in metaphase and interphase cells. In this case the different sequences are stained with different 'colors.' Such a staining pattern is that used in the examples of Section VIII of . . . this application." p. 32, lines 11-15.
135. The composition of claim 127 wherein one of said probes hybridizes to at least a portion of the last exon of the ABL gene and the other of said probes hybridizes to at least a portion of exon I of the BCR gene.	"The ABL probe on chromosome 9, c-hu-ABL, is a 35-kb cosmid (pCV105) clone selected to be telomeric to the 200-kb region of ABL between exons IB and II in which the breaks occur. The BCR probe on chromosome 22, PEM12, is an 18-kb phage clone (in EMBL3) that contains part of, and extends centromeric to, the 5.8-kb breakpoint cluster region of the BCR gene in which almost all CML breakpoints occur." p. 115, lines 11-16. *see also* Figure 8.
136. The composition of claim 134 wherein the chromosomal aberration is further defined as comprising a translocation, said translocation formed by breakpoints which occur on the long arms of chromosomes 9 and 22.	"The approach in such examples is based on FISH with probes from chromosomes 9 and 22 that flank the fused BCR and AL sequences in essentially all cases of CML (Figure 8)." p. 47, line 26 - p. 48, line 2.

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
137. The composition of claim 136 wherein the translocation breakpoints are further defined as occurring at the locations designated t(9;22)(q11;q34).	"Such reagents are exemplary of disease specific, in this case tumor specific, probes which can be labeled, directly and/or indirectly, such that they are visualizable when bound to the targeted chromosomal material, which in the case of CML is the vicinity of the translocation breakpoint regions of chromosomal regions 9q34 and 22q11 known to be associated with CML." p. 47, lines 12-16.
138. The composition of claim 137 wherein the translocation breakpoints are further defined to occur in the BCR and ABL genes respectively, and a fusion gene is formed by the translocation, and said fusion gene comprises portions of the BCR and ABL genes.	"The approach in such examples is based on FISH with probes from chromosomes 9 and 22 that flank the fused BCR and AL sequences in essentially all cases of CML (Figure 8)." p. 47, line 26 - p. 48, line 2.
139. The composition of claim 132 wherein the cells comprise a sample of human tissue.	"Human metaphase spreads were prepared . . ." p. 90, lines 9-10
140. The composition of claim 139 wherein the human tissue sample comprises peripheral blood.	"Sample Preparation: CML-4: Peripheral blood was centrifuged for 5 min. Ten drops of interface was diluted with PBS, spun down, fixed in methanol/acetic acid (3:1), and dropped on slides." p. 116, lines 23-25
141. The composition of claim 139 wherein the human tissue sample comprises bone marrow.	"Sample Preparation: . . . CML-2,3,7: Five to 10 drops of marrow diluted with PBS to prevent clotting were fixed in methanol/ acetic acid (3:1), and dropped on slides." p. 116, line 23 p. 117, line 1.
142. The composition of claim 131 wherein the cells comprise a sample of cultured cells.	"Metaphase spreads were prepared from methotrexate synchronized cultures according to the procedures of Harper et al. PNAS (USA) 78: 4458-4460, (1981)." p. 99, lines 21-23.

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
143. The composition of claim 127 wherein one of said probes hybridizes to the major breakpoint cluster region (M-bcr) of chromosome 22.	"The BCR probe on chromosome 22, PEM12, is an 18-kb phage clone (in EMBL3) that contains part of, and extends centromeric to, the 5.8-kb breakpoint cluster region of the BCR gene in which almost all CML breakpoints occur." p. 115, lines 13-16.
144. The composition of claim 127 wherein one of said probes hybridizes to the first exon of the BCR gene.	
145. The composition of claim 127 wherein one of said probes hybridizes to the last exon of the ABL gene.	"The ABL probe on chromosome 9, c-hu-ABL, is a 35-kb cosmid (pCV105) clone selected to be telomeric to the 200-kb region of ABL between exons IB and II in which the breaks occur." p. 115, lines 11-13
146. The composition of claim 138 wherein the presence of said fusion gene is diagnostic or prognostic for acute lymphocytic leukemia (ALL).	"the diagnosis and study of acute lymphocytic leukemia (ALL) may be accomplished by replacing the BCR probe (PEM12) of section VIII with a probe from the 5' end of the BCR gene. ALL is of particular interest because the Ph^1 chromosome is the most common cytogenetic abnormality in that disease, and the presence of such a chromosome is indicative of a very aggressive neoplasm." p. 49, lines 7-13.
147. The composition of claim 138 wherein the presence of said fusion gene is diagnostic or prognostic for chronic myelogenous leukemia (CML).	"This invention still further provides methods and reagents for producing staining patterns in a patient who is afflicted with a disease associated genetic rearrangement, such as those associated with the BCR-ABL fusion in CML . . . Such staining patterns can be useful in monitoring the status of such a patient . . . and can be predictive of a disease recurrence for a patient that is in remission." p. 20, line 25 - p. 21, line 7.

Claims added by This Amendment	**Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]**
148. A kit for the detection of chromosomal aberrations,	"This invention also provides for test kits comprising high complexity probes for the detection of genetic rearrangements, and specifically for those producing the BCR-ABL fusion characteristic of CML." p. 25, lines 14-18.
comprising a first and second nucleic acid probe, each labeled with a distinguishable label,	"In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of nucleic acid fragments, each fragment having a substantial fraction of its sequences substantially complementary to a portion of the nucleic acid for which specific staining is desired - the target nucleic acid, preferably the target chromosomal material. In general, the nucleic acid fragments are labeled by means as exemplified herein and indicated infra." p. 18, lines 14-20. "Section III *infra* describes methods of rendering the probe visible. Since multiple compatible methods of probe visualization are available, the binding patterns of different components of the probe can be distinguished – for example, by color. Thus, this invention is capable of producing any desired staining pattern on the chromosomes visualized with one or more colors (a multi-color staining pattern) and/or other indicator methods." p. 36, lines 17-23.

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
said first probe that specifically hybridizes to a part of the ABL gene on one side of said chromosomal aberration and said second probe that specifically hybridizes to a part of the BCR gene on the other side of said chromosomal aberration,	"Specifically herein exemplified are chromosome specific reagents and methods to detect genetic rearrangements . . . that produce the BCR-ABL fusion which is diagnostic for chronic myelogenous leukemia (CML). Such chromosome specific reagents for the diagnosis of CML contain nucleic acid sequences which are substantially homologous to chromosomal sequences in the vicinity of the translocation breakpoint regions of chromosomal regions 9q34 and 22q11 associated with CML. Those reagents produce a staining pattern which is distinctively altered when the BCR-ABL fusion characteristic of CML occurs. Figure 11 graphically demonstrates a variety of staining patterns which, along with other potential staining patterns, are altered in the presence of a genetic rearrangement, such as, the BCR-ABL fusion." p 19, line 22 - p 20, line 8.
wherein said probes hybridize to an aberrant chromosome	"Such nucleic acid probes preferably comprise nucleic acid sequences that are substantially homologous to nucleic acid sequences in chromosomal regions that flank . . . breakpoints associated with genetic rearrangements." p. 19, lines 14-18
wherein said probes are of sufficient length to be specifically detected in cytogenetic analysis.	"The terms 'staining' or 'painting' are herein defined to mean hybridizing a probe of this invention to a genome or segment thereof, such that the probe reliably binds to the targeted chromosomal material therein and the bound probe is capable of being visualized." p 36, lines 9-12

Claims added by This Amendment	Exemplary Support in U.S. Application Serial No. 07/537,305, filed June 12, 1990[1]
149. The composition of claim 127 wherein the aberrant chromosome is the Philadelphia chromosome.	"Fusion of the proto-oncogene c-ABL from the long arm of chromosome 9 with the BCR gene of chromosome 22 is a consistent finding in CML. That genetic change leads to formation of a BCR-ABL transcript that is translated to form a 210 kd protein present in virtually all cases of CML. In 90% of the cases, the fusion gene results from a reciprocal translocation involving chromosomes 9 and 22 producing a cytogenetically distinct small acrocentric chromosome called the Philadelphia (Ph^1) chromosome, Fig. 8." p. 17, lines 1-8. "Particularly described herein is the application of chromosome specific reagents and methods for detecting genetic rearrangements that produce the BCR-ABL fusion associated with CML." p. 47, lines 9-11.

Patent
Serial No. 09/765,291
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1. PRELIMINARY AMENDMENT.

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Registration No. 39,300

Date: February 15, 2001